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Are There Thresholds for Carcinogenesis?[a]

The Thorny Problem of Low-Level Exposure

ARTHUR C. UPTON

Institute of Environmental Medicine
New York University Medical Center
New York, New York 10016

INTRODUCTION

Few issues in health policy are more contentious than the choice of the appropriate dose–incidence model for use in estimating the risks of cancer associated with low-level exposure to a carcinogen. The notion that there may be no threshold for carcinogenic effects—namely, that some degree of risk may be associated with the lowest dose of carcinogen—seems to contradict everyday experience that teaches us that essentially no other type of insult produces a lasting injury unless it exceeds some threshold of severity.

In the past, toxicological risk assessments have traditionally been based on the concept of a no-effect level. The applicability of this concept to mutagenic effects, however, came to be questioned by the middle of the century.[1] Since then, the applicability of the concept to carcinogenic effects—which likewise may conceivably be mediated through effects on individual cells, rather than groups of cells—also has been challenged.

In principle, of course, it is not possible to prove or disprove the existence of an absolute threshold for carcinogenesis. Hence the argument for or against the threshold hypothesis must be based on theoretical as well as empirical evidence.[2] Some of the salient lines of evidence are summarized briefly in the following.

BIOLOGY OF CARCINOGENESIS

Unicellular, Monoclonal Origin of Cancer

The monoclonal origin of cancer is suggested by enzymological studies of human tumor cells, in which X-linked glucose-6-phosphate dehydrogenase has been used as a marker.[3] Similar evidence has come from studies of chemically induced tumors of chimeric mice, in which glucose phosphate isomerase has been used as a marker.[4,5] Cytogenetic analysis of tumor cells has also suggested their monoclonal nature.[6]

The evidence that cancer usually originates from a single precursor cell implies, as does the heritable nature of the malignant phenotype, that appropriate damage to one cell alone may suffice to increase the probability of the disease in a

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suitably susceptible individual. The data also indicate, however, that more than one alteration is necessary to convert a normal cell into a cancer cell, as discussed below.

Multicausal, Multistage Nature of Carcinogenesis

Clinical, pathological, and experimental data imply that cancer evolves through at least three successive stages: initiation, promotion, and progression.[7]

Initiation

Initiation, which starts the process, does not itself suffice to cause neoplasia but predisposes the affected cell and its progeny to subsequent steps in carcinogenesis. The initiated cell may not be recognizable as such, however, or may never form a tumor, unless it is further altered by subsequent tumor-promoting stimulation. The mechanism of tumor initiation remains to be established, but some type of mutational process is suggested by the evidence that 1) initiation is relatively prompt and irreversible; 2) most ultimate carcinogens are mutagens; 3) the frequency of cell transformation induced by a given carcinogen usually is highest if exposure to the agent occurs just before or during the DNA synthetic phase of the cell cycle[8]; 4) DNA to which a chemical carcinogen is bound can serve as a template for DNA replication[9]; 5) after exposure to a carcinogen, DNA synthesis and subsequent cell division "fix" the potential for neoplastic change[10]; 6) in a given biological system, the carcinogenic potency of an initiating chemical is generally correlated with the extent to which it binds covalently to DNA, and with the nature of the resulting reaction products; and 7) susceptibility to cancer is increased in persons who are deficient in DNA repair.[11] The frequency of neoplastic transformation is far higher, however, than that of single gene mutation in cells exposed to genotoxic carcinogens[12,13]; hence, the data implicate multiple oncogenic sites, damage of the genome at sites unlikely to be repaired (for example, tandem repeats), or genetic damage other than point mutations.[14] The specific genes that may be involved are only beginning to be defined but appear to include antioncogenes as well as oncogenes.[11] It is noteworthy, furthermore, that activation and expression of more than one oncogene appears to be necessary for cell transformation *in vitro*.[15]

Tumor Promotion

Tumor promotion is the process that results in the additional change, or changes, necessary to cause the neoplastic transformation of an initiated cell. In contrast to initiation, which can result from a single exposure to an appropriate tumor-initiating agent, tumor promotion requires repeated and sustained stimuli. Although tumor promotion has been demonstrated in a number of tissues, its mechanisms have thus far been studied systematically only in a few model systems. In one of these, the mouse skin model, nanomolar concentrations of the tumor-promoting phorbol ester 12-0-tetradecanoylphorbol-13-acetate induce stimulation of 1) macromolecular synthesis; 2) hyperplasia; 3) polyamine synthesis; 4) prostaglandin synthesis; 5) protease production; 6) alterations of cell membrane enzymes and glycoproteins; 7) induction of sister-chromatid exchanges; 8) altered

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differentiation; and 9) modified responses to other growth-controlling factors.[16] Such effects have also been demonstrated, *in vivo* and *in vitro*, in cells of various other species, including man. As yet, however, it is not known whether any of these responses is critical for tumor promotion. Furthermore, although all tumor-promoting agents induce cellular proliferation in their respective target tissues, each appears to be relatively tissue-specific. The capacity of the promoters to induce pleiotropic effects at nanomolar concentrations and their discrete structure-activity relationships implicate a hormone-like mode of action.[17–19]

Agents that possess initiating activity as well as promoting activity can cause neoplasia by themselves if given in sufficient doses. The effects of such "complete" carcinogens can be enhanced, however, by various other agents that are not active by themselves but can potentiate the effects of carcinogens if given simultaneously with them.[20] Such "co-carcinogens," which include certain phenols, aliphatic hydrocarbons, and aromatic hydrocarbons, are prevalent in the environment and appear to act by altering the uptake, distribution, and/or metabolism of carcinogens, or by enhancing the susceptibility of the target cells or host.[20] Tumor promoters have thus traditionally been considered to act predominantly through epigenetic mechanisms.[18] Recently, however, the production of indirect damage to DNA, resulting in mutations and chromosome aberrations, has been implicated in a growing number of instances[21–23]; for example, target organ-specific DNA adducts have been identified in association with the carcinogenic effects of diethylstilbesterol on the hamster kidney.[24]

Tumor Progression

Tumor progression is a process through which successive alterations in neoplastic cells give rise to increasingly autonomous clonal derivatives.[25] The precise nature of such alterations remains to be determined, but mutations and chromosome aberrations have been tentatively implicated.[7] Tumor progression may be accelerated by repeated exposure of neoplastic cells to carcinogenic stimuli or by selection pressures that favor the outgrowth of increasingly autonomous subpopulations of cells.

EPIDEMIOLOGIC DATA ON DOSE–INCIDENCE RELATIONSHIPS IN HUMANS

In contrast to the hundreds of chemicals that have been observed to possess oncogenic activity in laboratory animals, less than three dozen are known to induce cancer in man.[26] In few cases, moreover, are the relevant epidemiological data adequate to characterize the relationship between cancer incidence and the dose of a given carcinogen, except in a semiquantitative way.

Analysis of the dose–incidence relationship is less difficult with ionizing radiation than with carcinogenic chemicals because dosimetry with radiation is not complicated in the same way by pharmacokinetic variables. Furthermore, incidence data for irradiated populations are available over a wide range of radiation doses,[27,28] whereas comparable dose–incidence data for chemicals are generally lacking. In no case, however, do the data suffice to define the dose–incidence relationship in the low dose domain or to exclude the possibility of a threshold. Hence assessment of the carcinogenic risk associated with low-level exposure to

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any carcinogenic agent must depend on extrapolation from observations at higher dose levels, based on assumptions about the relevant dose–incidence relationships and mechanisms of carcinogenesis.

The extrapolation models generally used for estimating the carcinogenic risks of low-level irradiation are of the nonthreshold type; that is, the linear nonthreshold model or the "linear–quadratic" nonthreshold model is usually used.[28,29] The strongest epidemiological evidence in support of these models consists of (1) the large excess of acute leukemia and other juvenile malignancies that is associated with a dose as low as 1–5 rad *in utero*[30,31]; (2) the excess of thyroid

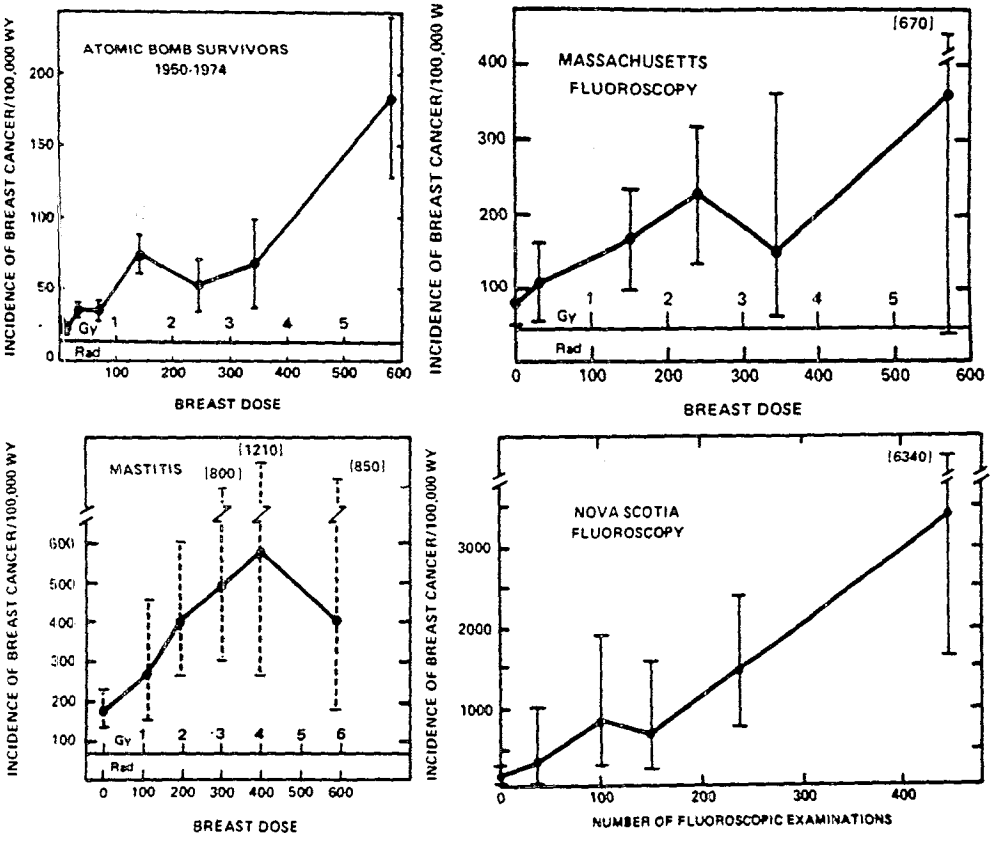

FIGURE 1. Incidence of cancer of the female breast as a function of dose in A-bomb survivors, in women treated with X-rays for acute postpartum mastitis, and in women subjected to multiple fluoroscopic examinations of the chest during treatment of pulmonary tuberculosis with artificial pneumothorax. (Reproduced from Boice *et al.*[34] with permission from the Radiological Society of North America.)

tumors that occurs following epilating irradiation of the scalp for tinea capitis in childhood, which is associated with an average dose to the thyroid gland of only 6–8 rad;[32,33] (3) the excess of breast cancers (FIG. 1) in (*a*) women exposed to A-bomb radiation, (*b*) women given therapeutic irradiation for postpartum mastitis, (*c*) women who received multiple fluoroscopic examinations of the chest during the treatment of pulmonary tuberculosis with artificial pneumothorax, and (*d*) women exposed occupationally to external gamma radiation in the painting of

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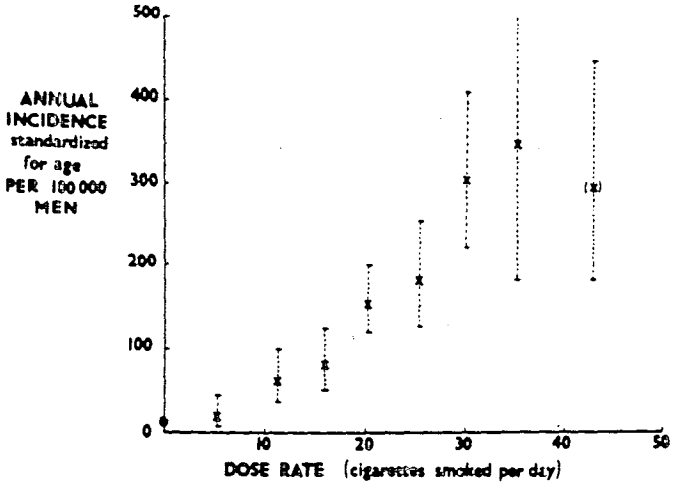

FIGURE 2. Incidence of lung cancer in regular smokers of cigarettes in relation to the number of cigarettes smoked per day. (Reproduced from Doll[35] with permission.)

luminous clock and instrument dials, which is similar in all four groups, irrespective of the marked differences among the groups in the duration of exposure[28,34]; and (4) the excess of leukemia in A-bomb survivors, which is evident at doses below 0.25 Gy.[28,29] The data from each of these studies, although not adequate to precisely define the shape of the dose–incidence curve in the low dose domain, are compatible with linear nonthreshold functions for each of the neoplasms in question.

With respect to the carcinogenic effects of chemicals, as opposed to ionizing radiation, quantitative dose–incidence information for human populations is far more limited. Nevertheless, considerable information is available for a few chemicals, one of them being cigarette smoke, which contains thousands of compounds, including initiating agents as well as promoting agents. In cigarette smokers, the incidence of lung cancer (FIG. 2) increases as a function of the average number of cigarettes smoked per day raised to a power of 1.8.[36]

Similarly, in chemists who were employed as distillers of 2-napthylamine, the cumulative incidence of cancer of the urinary bladder increases steeply with the duration of occupational exposure, approaching 100% in those who were exposed for 5 years or longer (FIG. 3).

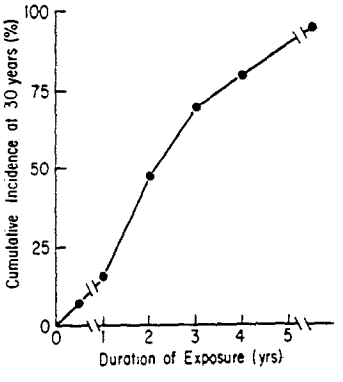

FIGURE 3. Cumulative incidence of tumors of the urinary bladder, at 30 years after start of exposure in 78 distillers of 2-naphthylamine and benzidine, in relation to duration of occupational exposure. (Reproduced from Saffiotti[37] [based on data from Williams[38]] with permission from the International Agency for Research on Cancer.)

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In asbestos workers, likewise, the incidence of lung cancer and of mesothelioma appears to increase linearly with the intensity and duration of exposure.[39] It is noteworthy, furthermore, that in cigarette smokers who have also been exposed occupationally to asbestos, the carcinogenic effects of cigarette smoke and asbestos appear to interact multiplicatively rather than additively (TABLE 1).

Also noteworthy is the fact that the excess of lung cancer in ex-smokers decreases rapidly after cessation of smoking,[41] suggesting that cigarette smoke affects primarily on late stages of carcinogenesis, acting as a promoting agent. This situation contrasts sharply with that in irradiated[28] or asbestos-exposed[42] populations, in whom the risk of lung cancer persists long after exposure.

EXPERIMENTAL DOSE–EFFECT DATA

Carcinogenesis in Laboratory Animals

The neoplasms induced experimentally in animals of different species vary widely in dose–incidence relationships. Although neoplasms of virtually every

TABLE 1. Age-Standardized Lung Cancer Death Rates for Cigarette Smoking, Occupational Exposure to Asbestos Dust, or Both

Group	Exposure to Asbestos?	History of Cigarette Smoking?	Death Rate	Mortality Difference	Mortality Ratio
Control	No	No	11.3	0.0	1.00
Asbestos workers	Yes	No	58.4	+47.1	5.17
Control	No	Yes	122.6	+111.3	10.85
Asbestos workers	Yes	Yes	601.6	+590.3	53.24

NOTE: Age-standardized lung cancer death rates are rates per 100,000 man-years standardized for age on the distribution of the man-years of all the asbestos workers. Number of lung cancer deaths based on death certificate information. (Adapted from Selikoff.[40])

type have been induced in one experiment or another, all types of neoplasms are not elicited in animals of any one species or strain. In fact, certain types of neoplasms actually decrease in frequency with increasing dose of whole-body irradiation (FIG. 4).

Among chemically induced neoplasms, the observed variations are attributable in part to pharmacokinetic differences affecting the dosage of carcinogen to different cells and subcellular targets. Such an explanation cannot account, however, for the observed variations in dose–incidence relations among radiation-induced neoplasms, which remain largely unexplained. Because of the multicausal, multistage nature of carcinogenesis, and the fact that the mechanism of carcinogenic effects is not the same in all instances, some diversity of dose–incidence relationships is to be expected.

Obviously, the observed dose–incidence curves cannot all be represented by the same mathematical function. Nevertheless, the following generalizations emerge from the data: (1) a carcinogenic-induced elevation in the age-specific incidence of a particular neoplasm may or may not result in an increase in the final cumulative incidence of tumors, depending on the survival of the population at risk; (2) chemicals differ greatly in carcinogenic effectiveness, with the result that

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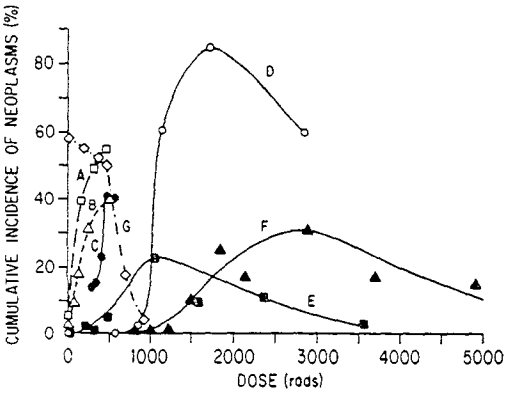

FIGURE 4. Dose–incidence curves for different neoplasms in animals exposed to external radiation: **(A)** myeloid leukemia in X-irradiated mice (Upton *et al.*[43]); **(B)** mammary gland tumors at 12 months in gamma-irradiated rats (Shellabarger *et al.*[44]); **(C)** thymic lymphoma in X-irradiated mice (Kaplan and Brown[45]); **(D)** kidney tumors in X-irradiated rats (Maldague[46]); **(E)** skin tumors in alpha-irradiated rats (percentage incidence × 10) (Burns *et al.*[47]); **(F)** skin tumors in electron-irradiated rats (percentage incidence × 10) (Burns *et al.*[47]); and **(G)** reticulum cell sarcoma in X-irradiated mice (Metalli *et al.*[48]). (Modified from reference 49. Reproduced from Upton[21] with permission from the Elsevier/North-Holland Publishing Company.)

the daily dose required to double the risk of neoplasia varies among different chemicals by more than six orders of magnitude (FIG. 5); (3) with ionizing radiation, the dose–incidence curve for high linear energy transfer radiation generally rises more steeply with dose and is less dependent on the dose rate than is the curve for low linear energy transfer radiation[54]; (4) for many types of neoplasms, the incidence passes through a maximum at some intermediate dose and decreases with further increase in the dose (FIG. 4); (5) the median time of tumor

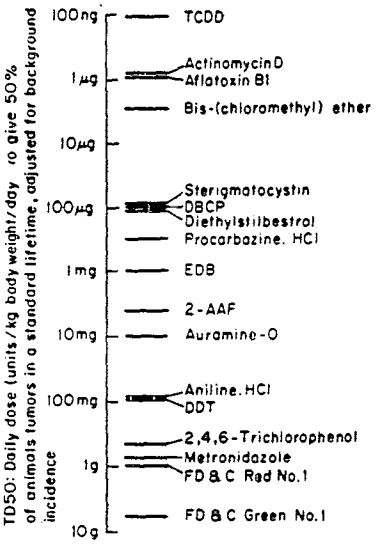

FIGURE 5. Range of carcinogenic potency in male rats. (Reproduced from Gold *et al.*[50] with permission from the National Institute of Environmental Health Sciences.)

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appearance t under conditions of daily exposure tends to vary inversely with the daily dose d according to the function

$$dt^n = \text{constant} \quad (1)$$

where n is greater than one[55]; (6) because radiation or a given chemical can often influence carcinogenesis through more than one mode of action, at least at high dose levels, the dose–incidence curve may reflect a combination of initiating effects, promoting effects, and anticarcinogenic effects, depending on the particular agent, dose, and exposure conditions; (7) the combined effects of different agents may be additive, synergistic, or antagonistic, depending on the agents in question and the conditions of exposure[56]; (8) at low-to-moderate dose levels, the effects of a complete carcinogen can generally be accentuated by appropriate tumor-promoting stimuli, which unmask initiating effects of the carcinogen that would otherwise remain unexpressed; and (9) under conditions in which initiating

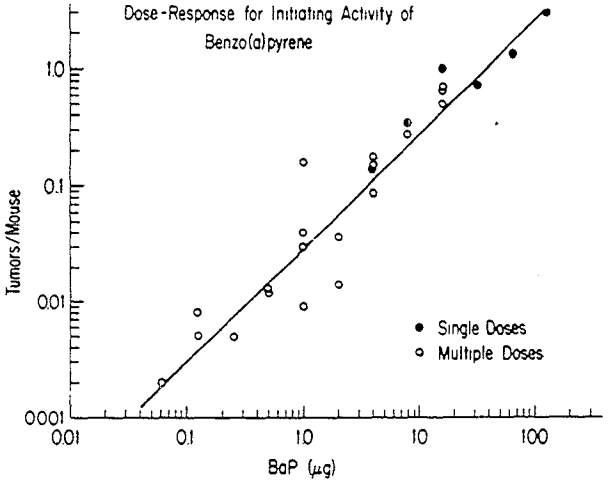

FIGURE 6. The yield of skin papillomas per mouse versus dose per application, after single and multiple doses of benzo-[*a*]pyrene. After treatment, 5 μg of 12-*O*-tetradecanoylphorbol-13-acetate was typically applied three times per week. (Reproduced from Burns and Albert[51] with permission from Mary Ann Liebert, Inc.)

effects are promoted to full expression, they generally increase as a linear nonthreshold function of the dose of the initiating agent (FIG. 6).

A number of experiments have been carried out with laboratory animals to characterize the dose–incidence curve in the low dose domain. In the largest of the experiments to date, performed with BALB/c female mice exposed to 2-acetylaminofluorine in the diet, the incidence of hepatomas increased as a linear nonthreshold function of the daily dose, whereas the dose–incidence curve for tumors of the urinary bladder approached a quasithreshold and resembled a hockey stick in shape (FIG. 7). Comparably large experiments have not been carried out with ionizing radiation, but the combined results of a number of sizable studies in mice, rats, and dogs imply that for most types of tumors (malignant as well as benign) the carcinogenic effectiveness per unit dose of X-rays and gamma rays is generally reduced at low doses and low dose rates, whereas that of high linear energy transfer radiations remains constant or may even be enhanced at low doses and low dose rates (FIG. 8), arguing against the likelihood of a threshold in such instances.[27,57,58]

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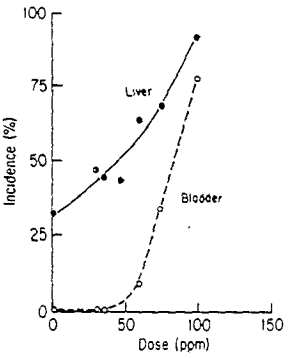

FIGURE 7. Cumulative incidence of neoplasms of the liver and urinary bladder in female BALB/c mice exposed to 2-acetylaminofluorine at various concentrations in the diet for up to 33 months. (Reproduced from Littlefield *et al.*[52])

Cell Transformation in Vitro

The neoplastic transformation of cells *in vitro* is not a perfect model of carcinogenesis *in vivo*, but the two systems have enough features in common at the cellular level so that cell transformation can be exploited to identify carcinogenic agents and explore their mechanisms of action. Although few detailed dose–response curves for cell transformation have been published, the effects of benzo[*a*]pyrene and ionizing radiation have been studied systematically. With benzo[*a*]pyrene, the logarithm of the frequency of morphological transformation in Syrian hamster embryo cells increases linearly with the logarithm of the dose[59,60]; the slope of the dose–effect curve suggests a one-hit model for this response except at the highest doses, where the deviation from linearity is attributable to cytotoxicity.[61] A one-hit model also holds for transformation by the combined effects of X-rays and benzo[*a*]pyrene.[61]

For Syrian hamster embryo cells transformed by X-rays, the logarithm of the transformation frequency per surviving Syrian hamster embryo cell appears to increase curvilinearly with the logarithm of the dose from 1 rad to 150 rad, but a linear response with a slope of one cannot be excluded. It is noteworthy, furthermore, that an increase in the frequency of cell transformation is detectable at a dose of only 1 rad.[62] Dose–response curves for X-ray-induced transformation of C3H 10T1/2 cells show an exponential increase in transformation frequency (foci per surviving cell),[63,64] with a doubling dose that is higher (about 100 rad) than the doubling dose in hamster cells (about 10 rad).

The effects of fractionating or protracting the dose of radiation vary with the experimental conditions in question. With a total dose of less than 100 rad, fractionation has been observed to enhance its transforming effectiveness,[65–67] whereas the opposite effect has been observed with higher doses (300–800 rad).[63,64,66,67] The transforming effectiveness of gamma radiation has generally

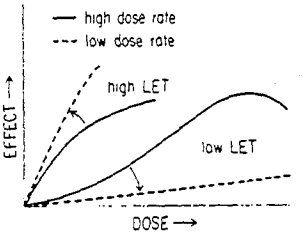

FIGURE 8. Dose–response curves depicting the incidence of tumors in laboratory animals in relation to the dose and dose rate of high and low linear energy transfer radiation. (Reproduced from Thomson *et al.*[53] [also in Updon *et al.*[54]].)

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been observed to diminish with protraction whereas that of high linear energy transfer radiation has been enhanced.[69]

Few comparable split-dose experiments have been performed with chemicals. Two doses of *N*-acetoxy-2-fluorenylacetamine administered 2–24 hr apart, however, were observed to yield a higher frequency of transformation with Syrian hamster embryo cells than the same total dose administered at once. In contrast, methyl-*N'*-nitro-*N*-nitrosoquanidine, mitomycin C, and ultraviolet light were less effective if delivered in split doses than in a single dose. The effectiveness of methyl methanesulfonate was unaffected by dose fractionation.[70]

The morphological transformation of C3H 10T1/2 cells *in vitro*, like that of cells *in vivo*, is not a one-step process. The first step appears to be rapid event,[71] occurring with one-hit kinetics in a high percentage of carcinogen-exposed cells.[72–74] The second step appears to be either a further qualitative change, occurring at a low frequency during the growth or confluence of the cells,[73–76] or an amplification of the transformed phenotype, possibly by release of the cells from inhibitory effects of neighboring nontransformed cells.[72,77,78] Clearly, further data will be needed to elucidate the mechanism of *in vitro* transformation and its relevance to carcinogenesis *in vivo*.

Mutations and Chromosome Aberrations

In view of the putative roles of mutations and chromosome aberrations as mechanisms of carcinogenesis, the dose–response relationships for these changes must be considered in assessing the risks associated with low-level exposure to carcinogens.

The changes in DNA that are induced by ionizing radiation and genotoxic chemicals, which include single-strand and double-strand breaks, base alterations, cross-linkage, and other modifications, can result from traversal of the cell nucleus by a single ionizing particle[79] or from interaction of the DNA with a single electrophilic molecule.[80,81] Although a dose of low linear energy transfer radiation that is lethal to 50% of dividing cells (that is, 2.5 Sv) causes hundreds of DNA strands breaks per cell, much of the damage is reparable, depending on the effectiveness of the cell's repair processes.[79] Such homeostatic repair processes are thought to enable the average cell to repair thousands of lesions in its DNA that occur "spontaneously" each day through the effects of natural background radiation, free radicals, and other degradative processes.[82,83] In spite of repair, however, the persistence of residual damage or the occurrence of lesions resulting from misrepair can give rise to mutations or chromosome aberrations or both, the frequency of which will depend on the amount and severity of DNA damage.

The frequency of mutations at the guanine (hypoxanthine) phosphoribosyl transferase locus in human lymphocytes increases as a linear, nonthreshold function of the X-ray dose over the range from 50 to 220 mSv, amounting to about six mutations per 10^6 cells per Gy, whether the dose is delivered in several fractionated exposures or in a single brief exposure.[84]

In X-irradiated mouse spermatogonia *in vivo*, the frequency of specific locus mutations increases as a linear–quadratic function of the dose, amounting to approximately six mutations per 10^6 cells per locus per Sv at low-to-intermediate doses and dose rates; with fast neutrons, the frequency of mutations increases more steeply, as a linear nonthreshold function of the dose, and independent of the dose rate.[56]

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The frequency of chromosomal aberrations in human lymphocytes irradiated *in vitro* increases as a linear–quadratic nonthreshold function of the dose, approximating 0.1 aberration per cell per Sv in the low-to-intermediate dose region.[85] The dose required to double the frequency of aberrations in such cells can thus be calculated to approximate 0.05 Sv.[86] With high linear energy transfer radiation, the frequency of aberrations increases more steeply, as a linear nonthreshold function of the dose, and irrespective of the dose rate.[56,86]

Dose–response relationships for chemically induced mutations and chromosomal aberrations are less well defined than those for ionizing radiation, in part because of the greater diversity of types and mechanisms of chemically induced DNA damage. Chemical mutagenesis and clastogenesis involve complex processes, including pharmacokinetic variables (uptake, transport, distribution, and excretion), metabolic activation and detoxication, and various reactions leading to the production of DNA lesions and their subsequent repair–misrepair. Each of these steps may conceivably involve first-order kinetics at low doses and hence be linear, so that in principle the overall process may be linear and not approach a threshold. Even if mutagenesis at low dose levels involved only linear processes, the slope of the resulting dose–response relationship could be orders of magnitude shallower than the slope at high dose levels, so that the dose–response curve could appear to reach a threshold or a quasithreshold.[87] In fact, nonlinear mechanisms are likely to operate in at least some of the transport, metabolism, elimination, and repair processes that are involved in mutagenesis,[87] and it is noteworthy that a single step involving a threshold in such a sequence could give the overall process a threshold. Hence, in view of the complexity of the many processes involved in chemical mutagenesis, it is not astonishing that the dose–response curves for mammalian cells exposed *in vitro* have been observed to include responses that appear to involve linear nonthresholds as well as quasithresholds.[88] Whether any of the responses truly involves a threshold, however, cannot be determined from existing data.

Other factors complicating assessment of the practical implications of dose–response data for chemical mutagenesis are the fact that chemicals vary more than a millionfold in mutagenic potency and the fact that the magnitude of the variation among chemicals also differs depending on the types of cells and indices of mutagenicity in question.[88,89]

FACTORS MODIFYING THE DOSE RESPONSE

A variety of factors are known to affect dose–incidence relationships in carcinogenesis.[90] These include, among others, variables influencing the susceptibility of exposed individuals (for example, genetic background,[11] age at exposure,[28] immunological reactivity,[91] differences in DNA repair capacity,[85] and differences in drug metabolism[92,93]). The capacity to metabolize a chemical can vary among humans by more than 100-fold[94] and among species by more than 1000-fold.[93] In any one person, moreover, the balance between toxification and detoxification may be highly dose-dependent.[95] As a result, the effective dose of a substance to its biological target may differ substantially among persons at a given ambient exposure level.

Also of potential importance in modifying the dose–response relationship for a given carcinogen are the effects of other physical or chemical agents. The interac-

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tive effects of these agents may be additive, synergistic, or inhibitory, depending on the agents in question and the conditions of exposure.[56,96] In a number of instances, appropriate stimulation by a tumor-promoting agent has been observed to convert a curvilinear dose–incidence response involving a threshold into a linear response not involving a threshold (FIG. 9).

HEALTH POLICY IMPLICATIONS

The problem of risk assessment for purposes of public health policy is complicated by the fact that cancer arises through successive stages, each of which may be affected differently and in as yet unpredictable ways by a given agent. No single process is known to be applicable to all carcinogens, all types of cancer, and all persons at risk. Most multistage models assume, however, that 1) a normal cell must undergo two or more stochastic and essentially irreversible changes to become transformed into a cancer cell; 2) one or more of the changes may be inherited via the fertilized egg (zygote); and 3) it is the clonal proliferation of a

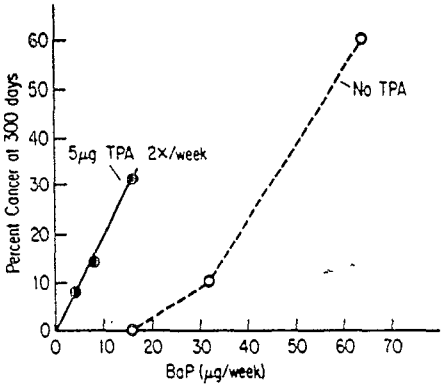

FIGURE 9. The incidence of carcinomas of the skin after 350 days of treatment in mice exposed to a weekly dose of benzo[*a*]pyrene on Monday, with or without 5.0 μg of 12-*O*-tetradecanoylphorbol-13-acetate on Wednesday and Friday. Doses refer to the amount of benzo[*a*]pyrene given per week. The treatments were started at 56 days of age. (Reproduced from Burns and Albert[51] with permission from Mary Ann Liebert, Inc.)

single cell in which all the necessary changes have occurred that ultimately gives rise to a cancer.[97] According to such a model, any agent that directly or indirectly increases the probability of any one of the changes may be a carcinogen because such an agent would increase the likelihood that a cell will ultimately acquire all of the changes necessary for transformation. The model also implies that the changes necessary for malignant transformation must occur in the proper sequence, because some carcinogenic stimuli act only on early stages while others act on later stages, and that carcinogens that affect different stages in the process can be multiplicative rather than merely additive in their combined effects.

In the absence of definitive human data, risk assessment must depend on other types of evidence (for example, on the results of bioassays in laboratory animals or on short-term tests for carcinogenicity). Under such circumstances, risk assessment is complicated by questions about 1) the reliability of the test system for predicting risks to humans (quantitatively as well as qualitatively); 2) the reproducibility of the test results; 3) the influence of species differences in pharmacokinetics, metabolism, hoemostasis, repair rates, life span, organ sensitivity, and baseline cancer rates; 4) the influence of differences in dose, dose rate, and routes

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of exposure; 5) the significance of benign, as opposed to malignant, tumors; 6) the precise nature of the dose–incidence relationship; and 7) the significance of negative results.

On the basis of present knowledge, the carcinogenicity of an agent for human tissue cannot be predicted accurately by extrapolation from animal data. A chemical that causes tumors in a particular organ of one species may cause tumors in another organ, or no tumors at all, in other species; for example, bioassay results in the mouse have been predictive for the rat in only about 80% of cases, and vice versa.[98,99] The problem is complicated further by the fact that the human population is exposed to myriads of agents interacting in various ways, whereas animals in the standard bioassay are ordinarily exposed to only one agent at a time.

The dose–incidence models used by national and international experts for estimating the carcinogenic risks of low-level ionizing radiation are generally of the nonthreshold type.[27–29,100] The models also allow, however, for the fact that the magnitude of risk per unit dose appears to vary with the form of cancer, sex, age at irradiation, type of radiation (linear energy transfer), dose, and dose rate. In view of these differences, each type of neoplasm is generally considered individually, with efforts to integrate insofar as possible all relevant epidemiological and experimental data.

Although the relation between incidence and radiation dose is known to vary from one type of neoplasm to another, the observed effects of dose rate and linear energy transfer on the dose–incidence relation generally conform to the patterns illustrated in FIGURE 8, which are consistent with those expected if one were to assume that carcinogenesis could be initiated in a suitably susceptible individual by a mutation or chromosomal aberration in a single somatic cell. According to this interpretation, the dose–incidence curve for high linear energy transfer radiation would be expected to conform, in general, to the expression

$$I = C + aDE^{-pD} \quad (2)$$

where I is the incidence at dose D, C is the incidence in nonirradiated controls, and a and p are constant coefficients; for low linear energy transfer radiation, the dose–incidence curve would conform, in general, to the expression

$$I = (C + aD + bD^2)e - (pD + qD^2) \quad (3)$$

where the symbols are comparable to those above, except for different values of the coefficients a and p and an additional coefficient q.[101]

Although many of the observed dose–incidence curves conform to the patterns described above, the curve for breast cancer appears more nearly linear, and the curve for osteosarcomas induced by radium-226 appears more nearly quadratic.[28] Because of the complex, multicausal, multistage nature of carcinogenesis, no one simple model is likely to characterize the dose–incidence relation over a wide range of doses and exposure conditions. At intermediate-to-high doses, a complete carcinogen can be expected to exert promoting effects as well as initiating effects on tumor formation through alterations in cell population kinetics and other changes. At still higher doses, the response can be expected to saturate because of cytotoxicity.

In view of uncertainty about the shape of the dose–incidence curve at low doses and low dose rates, various hypothetical models have been used in an effort to arrive at a range of estimates for assessing the risks of low-level radiation (FIG. 10) and chemicals (FIG. 11).

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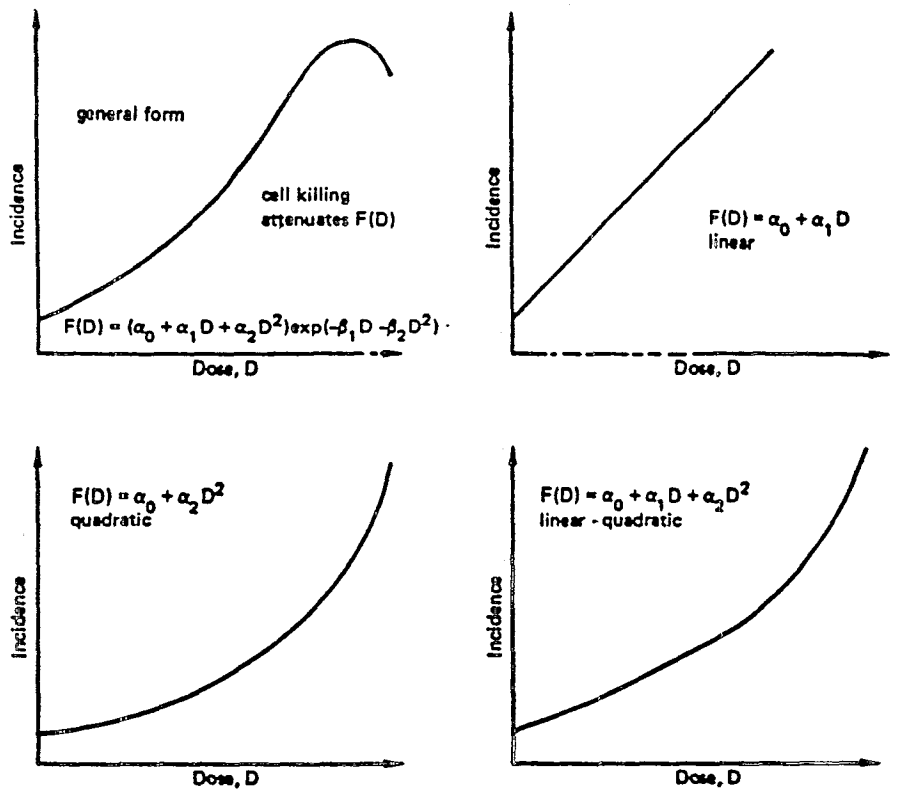

FIGURE 10. Dose–response curves for four different mathematical models relating cancer incidence to radiation dose. (Reproduced from Reference 28 with permission from the National Academy Press.)

Criteria to aid in the evaluation of epidemiological and experimental data on the carcinogenicity of chemicals have been formulated by the International Agency for Research on Cancer,[26] the Interagency Regulatory Liaison Group,[102] and the Office of Science and Technology Policy.[103] These criteria include definitions for weighing the adequacy of the data (for example, definitions of "sufficient evidence" and "limited evidence"[26]). In situations where there is sufficient evidence for the carcinogenicity of a chemical in laboratory animals but not in humans, the compound is assumed to present a carcinogenic risk to humans, although the magnitude of the risk cannot be estimated with precision.[26] Although bioassay and short-term "screening" tests may give information on the mode of action of a chemical, such tests are considered to provide no more than supporting evidence of carcinogenicity and not to provide sufficient evidence by themselves.

Estimation of carcinogenic risks on the basis of animal data, however good the animal data may be, is fraught with uncertainty. Although a chemical with carcinogenic potency in one species (such as aflatoxin B_1) is likely to be carcinogenic in another, the procedure for extrapolating across species involves assumptions about species differences in metabolism and appropriate scaling factors for dose and time. Various attempts have been made to determine correct scaling factors based on pharmacokinetic data,[95] but the question remains unresolved.

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In addition, a dose–response model must be used for interpolating between the lowest dose at which a significantly increased incidence has been observed and the baseline (zero dose) incidence. For this purpose, a linear, nonthreshold (one-hit) dose–incidence model is generally recommended, although such a model cannot be verified experimentally.[104] This type of model gives higher estimates, however, than other models (FIG. 10 and TABLE 2). Hence it is usually thought likely to overestimate the risk at low doses and is thus often considered to estimate the "upper limit" of risk.

Evidence concerning the modes of action of different classes of carcinogens (initiators, promoters, co-carcinogens, and complete carcinogens) suggests that a linear nonthreshold model may be appropriate only for initiating agents and complete carcinogens, whereas models yielding smaller estimates of risks at low doses might represent more accurately the dose–incidence relationships for other classes of carcinogens. For some types of carcinogens, thresholds might even be envisioned to exist because of relevant pharmacokinetic factors. For example, some chemicals that must be activated metabolically to become carcinogenic may be handled through nonlinear metabolic processes, with the result that thresholds for their carcinogenic effects may exist.[87] In addition, some agents may act through toxic or systemic effects that are produced only at high doses (for example, those causing carcinogenic effects on the mucosa of the urinary bladder in association with cystitis and urinary tract calculi,[106] or those acting through immunosuppressive effects.[91]

If it can be shown, however, that a chemical acts through mechanisms that are shared by agents that contribute to the baseline incidence of "spontaneously

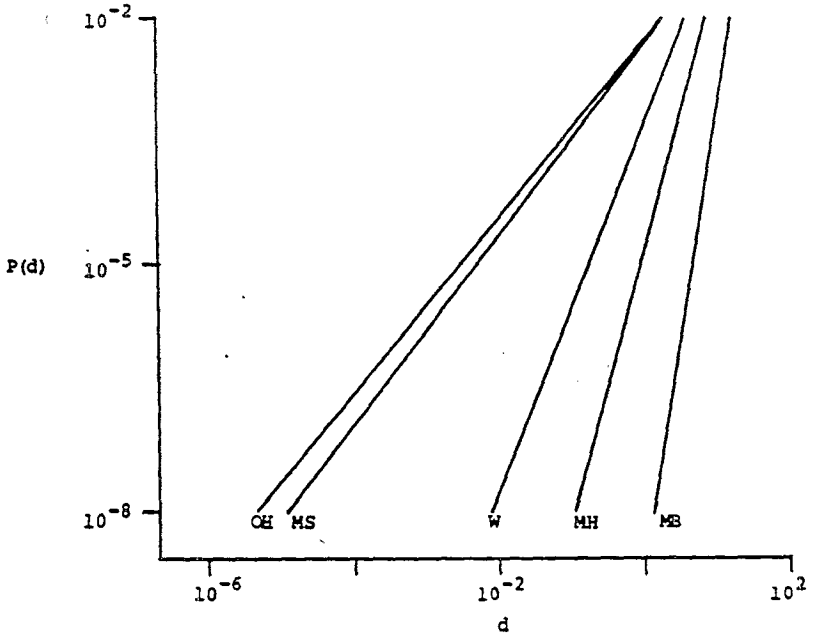

FIGURE 11. Estimated risk of liver cancer, P(d), in relation to dose of aflatoxin, d, as determined with different dose–incidence models. The models for the different curves are as follows: OH, one-hit model; MS, multistage model; W, Weibull model; MH, multihit model; MB, Mantel–Bryan (log-probit model). (Reproduced from Krewski and Van Ryzin[104] with permission from the Elsevier/North-Holland Publishing Company.)

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TABLE 2. Estimated Human Risks from Ingestion of 0.12 G/Day of Saccharin

Method of High- to Low-Dose Extrapolation	Lifetime Cases per Million Exposed	Cases per 50 Million per Year
Rat dose adjusted to human dose by surface area rule		
Single-hit model	1,200	840
Multistage model (with quadratic term)	5	3.5
Multihit model	0.001	0.0007
Mantel–Bryan probit model	450	315
Rat dose adjusted to human dose by mg/kg/day equivalence		
Single-hit model	210	147
Multihit model	0.001	0.0007
Mantel–Bryan probit model	21	14.7
Rat dose adjusted to human dose by mg/kg/ lifetime equivalence		
Single-hit model	5,200	3,640
Multihit model	0.001	0.0007
Mantel–Bryan probit model	4,200	2,940

NOTE: Adapted from Reference 105.

occurring" cancer, then exposure to only a small dose of the chemical can be expected to increase the incidence by some finite amount.[2,107–109] For this reason, the use of a nonthreshold model is generally recommended in risk assessment when the mode of action of the carcinogen in question is not known.

CONCLUSIONS

The possibility that there may be no threshold for the induction of some forms of cancer by ionizing radiation or certain chemicals, at least in appropriately susceptible individuals, is suggested by (1) evidence that most cancers arise from a single transformed cell; (2) the heritable nature of the transformed phenotype; (3) the association between neoplastic transformation and specific mutations or chromosomal aberrations; (4) the correlation between carcinogenicity and genotoxicity; (5) the nature of the observed dose–response relationships for mutations, chromosomal aberrations, and cell transformation *in vitro;* and (6) the nature of the dose–incidence relationships for certain neoplastic lesions *in vivo*.

At the same time, however, carcinogenesis appears to be a multistage process involving the stepwise evolution of increasingly autonomous cells in which the outcome is influenced by such variables as age, genetic constitution, physiological state, metabolism, and homeostatic interactions within and among tumor-forming cells and normal cells. Other variables that complicate analysis of dose–incidence relationships are (1) poorly defined interactions among cancer-causing agents, which may be additive, multiplicative, or antagonistic in their combined effects; (2) the fact that the human environment contains myriads of agents, many of which are known to modulate the effects of others; (3) the existence of nonlinear kinetics in the metabolism of certain chemical carcinogens; and (4) evidence that some agents act primarily through mechanisms that presumably operate only at high dose levels.

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Because of the complexity of carcinogenesis and the variability of dose–incidence relationships, it is not possible on the basis of present knowledge to extrapolate confidently across different species, population groups, doses, and conditions of exposure in estimating the carcinogenic risks of a particular carcinogen for human populations exposed at low dose levels. Agents differ widely in metabolism, potency, and mode of action, with the result that their hazards can be expected to vary greatly at low doses, whether estimated with the use of a threshold dose–incidence model or a nonthreshold dose–incidence model. In selecting the appropriate dose–incidence model for risk assessment, one must consider each agent individually, taking all relevant epidemiological, clinical, and experimental data into account.

The existing evidence does not rigorously exclude a threshold for any carcinogen, but the use of a nonthreshold model for ionizing radiation and most chemicals, especially those with genotoxic activity, is generally recommended on the basis of present knowledge. The choice of a threshold model cannot be justified in the absence of evidence that the metabolism or mode of action or both of the agent varies appropriately in relation to the dose.

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